



INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 20916WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/NL 03/00435	International filing date (day/month/year) 12.06.2003	Priority date (day/month/year) 17.06.2002
International Patent Classification (IPC) or both national classification and IPC C07D319/06		
Applicant DSM IP ASSESTS B.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 02.12.2003	Date of completion of this report 11.11.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Stroeter, T Telephone No. +49 89 2399-8088 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/NL 03/00435**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-5 as originally filed

Claims, Numbers

1-11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-11
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-11
Industrial applicability (IA)	Yes: Claims	1-11
	No: Claims	

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

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Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Prior art documents

Reference is made to the following documents. The given numbering will be adhered to in the rest of the procedure:

- D1: WO 02/06266 A (MINK DANIEL ;DSM NV (NL); KOOISTRA JACOB HERMANUS MATTHE (NL); MUL) 24 January 2002
- D2: WO 00/68221 A (EGYT GYOGYSZERVEGYESZETI GYAR ;VERECZKEYNE DONATH GYOERGYI (HU); B) 16 November 2000
- D3: GB 885 516 A (ARTHUR HENRY CLARKSON) 28 December 1961
- D4: MARCH J: "ALIPHATIC NUCLEOPHILIC SUBSTITUTION" ADVANCED ORGANIC CHEMISTRY. REACTIONS, MECHANISMS, AND STRUCTURE, NEW YORK, JOHN WILEY & SONS, US, 1992, page 392, XP002217003 ISBN: 0-471-60180-2
- D5: MURPHY C F, KOEHLER R. E.: "CHEMISTRY OF CEPHALOSPORIN ANTIBIOTICS. XVIII." J. ORG. CHEM., vol. 35, no. 7, 1970, pages 2429-2430, XP002252465

2 Novelty (Article 33(2) PCT)

The most related prior art appears to be D1 disclosing on page 5, last paragraph, a process wherein a carboxylic acid derivative of present formula (2) is transformed into the corresponding acid chloride, e.g. by use of oxalylchloride. Said acid chloride is then converted to the ester with a tertiary alcohol in the presence of a base. D1 also refers to the present stereochemistry (see page 2). Therefore D1 is a generic disclosure of the present invention but fails to mention the specific base N-methylmorpholine (NMM) as a base in the second reaction step. Consequently, the present process of claim 1 represents a novel selection of what has been disclosed in D1. Claims 1-11 are novel by consequence.

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3 Inventive step (Article 33(3) PCT)

The selection of NMM as a base appears to be an obvious solution to the problem of providing an alternative process for the preparation of the esters of formula (1). Reactions of the Schotten-Baumann type are widely used in organic chemistry whenever esters have to be prepared. The presence of a base is a necessary feature in these reactions (D3, D4). It is well known that aprotic, non-nucleophilic and weak bases are preferred in order to avoid the formation of amides, e.g. dimethylaminopyridine (D1), NMM (D3), pyridine (D3, D4) or triethylamine (D5). Therefore, in the absence of a specific unexpected effect, the present subject-matter of claims 1-11 lacks an inventive step.

Please note, that D2, page 7, 4th paragraph already states that "...ketale group would be resistant to organic acids under the reaction conditions used..." and thus no surprising effect can be assigned to the stableness of the present ketals under acidic conditions.

4 Industrial applicability (Article 33(4) PCT)

The subject-matter of the present set of claims 1 to 11 is in accordance with the requirements of Article 33(4) PCT.